REMARKS/ARGUMENTS

The Examiner has rejected claims 1-7 and 13-22 for failure to comply with 35 USC § 112. This rejection is obviated by the proffered amendments.

The Examiner poses a number of questions regarding operating details of the claimed process and asserts that without answers to such questions the application fails to comply with 112. This is clearly erroneous as there is no requirement that the specification or the claims serve as a production specification. *In re Gay*, 135 U.S.P.Q. 311 (C.C.P.A. 1962).

The claims define the method with reference to a trained, feedforward neural network that employ training and testing data that employ genetic mutation information that correlates with phenotypic change. The claimed method sets forth the training steps and the specification provides a description that enables one skilled in the art to make and use the method. See, e.g., page 29 *et. seq*. It also provides a would-be infringer with information sufficient to determine what is claimed from what is not. Nothing further is required and this rejection is overcome.

The Examiner has rejected claims 1-7 and 13-22 as anticipated by the Draghici reference. This rejection is respectfully traversed for the following reasons.

Even if the Draghici reference referred to every element of the instant invention it would not anticipate it. In order for a reference to anticipate a claimed invention, the reference must be enabling. Draghici is not such a reference.

Draghici refers to the use of a feedforward neural network to predict IC90 for arbitrary units at page 324. However, no description of the actual data input is provided nor is there is any description of the topology of the network beyond the mention of the number of hidden layers. Further, they refer to only 31 data units used to train the network. The

manner of training is unknown as is the composition and type of data that was input. One skilled in the art would not understand how to construct a feedforward neural network relating genetic mutation that correlates to phenotypic properties useful in predicting therapy resistance from this description. It is also worth noting that the authors themselves recognized that their approach was not enabling. Dragchi at page 324, line 3, *et. seq.* (discussing problems that make feedforward neural networks untenable under the circumstances of the study). This is also expressly recognized at page 324, section 4.2, in which Draghici describe the "alternative approach" that was explored throughout the study because the feedforward approach they took did not work. Accordingly, the reference is not enabling and should not be applied against the instant invention.

The Draghici reference does not disclose a method for predicting resistance of a pathogen to at least one therapeutic agent, using a feed forward neural network that relates genetic mutations to phenotypic change. Indeed, the entire reference is directed to the identification of connections and relationships between drug resistance and structural molecular changes of the HIV protease enzyme induced by mutations. As the authors state, "the aspects novel to our study include the use of *structural* information and the use of neural processing," Draghici at page 322, line 23 (emphasis added). In other words, the relationships that were explored involved examination of the protease protein structure in relation to the performance of the drug and not genetic mutation as in the instant application.

Starting from mutant genetic sequences, Dragichi modeled their corresponding 3-dimensional molecular protein structures together with the protease inhibitor, Indinavir, making use of a software package. By subsequently analyzing the 3-dimensional structures with Ligplot, they could calculate the number and strength of the bonds between the interacting atoms of the drug and the mutant, referred in the article as "contacts". The contacts were then used as the input data in a Kohonen neural network, and the output data being the grouping of the contacts by three ranges of IC90 fold resistance to Indinavir. Thus, the data inputs were not genetic mutations as in the instant application but, rather, were structural protein information.

With reference to the argument raised by the Examiner at page 4 of the Office Action, Draghici does not teach the construction of a training set that has patterns with fixed numbers of units so that a master list of mutants is compiled. Instead, it proposes the construction of a training set that has patterns with fixed numbers of units so that a master list of contacts, not mutants, is compiled. Such a master list of contacts is inferred from the adjacent phenotypic patterns. Draghici proposes a method for conceptualizing (clustering) "contacts" by their associated phenotypic resistance using a Kohonen neural network with a self-organized feature map (SOFM). Draghici at page 325, lines 3 and 15. This self-organizing map uses an unsupervised learning rule or function. This tool is used to separate the input data by behavioural patterns, in other words, separating the different contacts, which is the number and strength of a protease mutant's atomic interactions with Indinavir, by their corresponding IC90 fold resistance values.

The approach Draghici followed was sensible given the context of the the Draghici study but tells one nothing of how to predict resistance to a therapeutic agent based on genetic mutation as in the instant application.

Here too, it is also worth noting that even Draghici's description of the inapposite Kohnen network is not enabling as it lacks the provision of mathematical formulas, the description of the topology and hierarchical structures of the Kohonen neural network employed. These data are necessary to evaluate the validity of the proposed neural network.

Because the cited reference is not enabling and does not disclose (nor or even suggest) the claimed invention, this rejection is overcome and a notice of allowance is respectfully solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page(s) is/are captioned "Version with markings to show changes made".

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

2. (Twice Amended) A method for predicting resistance of a pathogen to at least one therapeutic agent comprising:

(a) providing a trained neural network that is trained by

i) using a training data set comprising members that correspond to at least one genetic mutation that correlate to a phenotypic change that cause a change in resistance of the pathogen to at least one therapeutic agent,

ii) propagating a training data set in a feed-forward fashion,

iii) calculating the associated error,

iv) back propagating the error,

vii) adjusting the weights in the neural network,

vi) minimizing the error function by repeating steps ii), iii), iv), v),

viii) using a testing data set to ensure proper training, said testing data set comprising members that correspond to at least one genetic mutation that correlate to a phenotypic change that cause a change in resistance of the pathogen to at least one therapeutic agent, which testing data set is different from the training data set;

(b) providing a determined genetic sequence from the pathogen by

i) obtaining a sample of said pathogen,

ii) obtaining the genetic sequence from the sample; and

(c) predicting resistance of the pathogen to the therapeutic agent using the determined genetic sequence and the trained neural network [to identify at least one mutation of the determined genetic sequence that confers resistance to the therapeutic agent].

13. (Twice Amended) A method for predicting resistance of a pathogen to a therapeutic agent comprising:

(a) providing a neural network;

(b) training a neural network on a training data set, wherein each member of the training data set corresponds to a genetic mutation that correlates to a phenotypic change that causes a change in therapeutic agent resistance of the pathogen, said training being performed by

i) propagating a training data set in a feed-forward fashion,

ii) calculating the associated error,

iii) back propagating the error,

iv) adjusting the weights in the neural network,

v) minimizing the error function by repeating steps i), ii), iii), iv),

vi) using a testing data set to ensure proper training, said testing data set comprising members that correspond to at least one genetic mutation that correlate to a phenotypic change that cause a change in resistance of the pathogen to at least one therapeutic agent, which testing data set is different from the training data set;

(c) providing a determined genetic sequence from the pathogen, by

i) obtaining a sample from said pathogen,

iii) obtaining the genetic sequence from the sample; and

(d) predicting resistance of the pathogen to at least one therapeutic agent using the determined genetic sequence and the trained neural network [to identify at least one mutation of the determined genetic sequence that confers resistance to the therapeutic agent].

20. (Twice Amended) A trained neural network capable of predicting resistance of a disease to a therapeutic agent, wherein the trained neural network comprises:

(a) a set of input nodes, wherein each member of the set of input nodes corresponds to a mutation in the genome of the disease;

(b) optionally a set or more of hidden nodes;

(c) a set of output nodes, wherein each member of the set of output nodes corresponds to the therapeutic agent used to treat the disease;

(d) and wherein the trained neural network is [was] trained by

i) using a training data set comprising members that correspond to at least one genetic mutation that correlate to a phenotypic change that cause a change in resistance of the pathogen to at least one therapeutic agent,

ii) propagating a training data set in a feed-forward fashion,

iii) calculating the associated error,

iv) back propagating the error,

v) adjusting the weights in the neural network,

vi) minimizing the error function by repeating steps ii), iii), iv), v),

using a testing data set to ensure proper training, said testing data set comprising members that correspond to at least one genetic mutation that correlate to a phenotypic change that cause a change in resistance of the pathogen to at least one therapeutic agent, which testing data set is different from the training data set.